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EXAMINER	
YU, MELANIE J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,528	SU ET AL.	
	Examiner	Art Unit	
	Melanie Yu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 1-33, in the reply filed on February 1, 2005 is acknowledged. Claims 34-37 have been withdrawn from further consideration as being drawn to a non-elected invention.

Claim Objections

2. Claim 5 is objected to because of the following informalities: the claims contain the acronyms "COIN" and "SERS" which need to be written out in their entirety. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Part a of claim 1 is vague and indefinite because it is unclear how the proteins are separated on the basis of chemical and/or physical properties. It is unclear if proteins with similar chemical and/or physical properties are separated from proteins that are dissimilar or rather the sample is separated into smaller samples with any chemical and/or physical properties. Regarding part b of claim 1, it is indefinite as to if the separated proteins maintained in a separated state are the same as the proteins of part a. It is also unclear whether in order to be separated at discrete locations on a solid substrate the proteins are deposited onto a solid

substrate. It is also unclear how the proteins are separated within a stream of flowing liquid and if there is more than one stream of flowing liquid to perform maintenance of protein separation. It is vague as to whether step c of detecting Raman spectra and part c of contacting the separated proteins are meant to occur in the same step. Within the detecting step of part c it is unclear whether the separated proteins are the separated proteins of part a or part b. It is also unclear how structural information is provided by the Raman spectra.

Claim 2 is vague because it is unclear what information regarding source of the sample is correlated with information of the Raman spectra.

Regarding claim 7, it is unclear if the denaturing or proteins comprises contacting proteins with a denaturing agent.

With respect to claim 15, the phrase "sequential discrete locations" is vague because it is unclear whether sequential refers to adjacent discrete locations detected simultaneously or whether discrete locations are detected in a predetermined order.

Claim 23 is vague because it is unclear what relation is correlated between the SERS spectra and the sample locations. It is vague as to whether the location of the sample is correlated with the SERS spectra or if some other characteristic of the sample is correlated with the SERS spectra.

Regarding claims 25 and 26, it is unclear how the proteins are maintained in a separated state, it is unclear whether the proteins are separated within the same stream. In claim 26, the stream of separated proteins mixes with a stream of metal colloids, and it is unclear whether the stream of metal colloids enters the stream of separated proteins or if the two streams converge and enter a common third stream. It is also unclear if SERS-active nanoparticles are formed with

the binding of protein to metal colloids. Furthermore, it is vague as to how the metal colloids enter separated portions of the stream of proteins.

4. Claim 1 recites the limitation "the protein content" in line 1 of the claim. Claim 7 recites the limitation "the denaturing agent" in line 1 of the claim. There is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-5, 10, 14-17, 20-26 and 29-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Natan et al. (US 6,579,721).

Natan et al. teach a method for analyzing the protein content of a biological sample (col. 10, lines 40-47 describe the sandwich assay; col. 10, line 52 describes the target analyte being a protein), comprising: separating proteins in a sample on the basis of chemical properties of the protein (separates target analyte based on chemical interaction, col. 23, lines 45-48); maintaining separated proteins in a separated state at discrete locations on a solid substrate (samples in each well are maintained without cross contamination, col. 25, lines 1-4); detecting a Raman spectra produced by the separated proteins at the discrete locations (each of the wells is individually addressed, col. 25, lines 1-4; and the microwell array can be used for SERS analytical techniques, col. 23, lines 58-61), wherein the spectrum provides information about the structure

of one or more particular proteins at the discrete location (Fig. 12 discloses a SERS detection before amplified proteins are added; detection of unique compounds by SERS, proteins, col. 24, lines 1-4); contacting the separated proteins with capture probes under conditions suitable to form a capture probe/protein complex at one or more of the discrete locations (col. 10, lines 58-64; at col. 13, lines 45-52 any one of the participants can be immobilized to the substrate surface, a ligand is then bound to the immobilized receptor, protein); contacting the complexes with a Raman-active probe construct that binds to the complex (col. 13, lines 45-52, an Au-conjugated antibody is conjugated with the ligand, which is bound to the immobilized receptor, protein); and detecting Raman spectra produced by the probe construct/protein complexes at the discrete locations, wherein the spectrum from a discrete location provides information about the structure of one or more particular proteins at the discrete location (col. 23, lines 58-61 discloses SERS detection; Fig. 12 discloses an amplified detection after an unamplified detection; furthermore a change in resonance is detected as the target is brought in contact with the Raman-active probe, therefore the SERS detection occurs before and after contacting the proteins with capture probes and Raman active probes, col. 18, lines 1-5).

With respect to claims 2-5, Natan et al. teach correlating information with information regarding the source of the sample (col.). Natan et al. also teaches the capture probe being a primary antibody that binds specifically to the protein in the complex (immobilized receptor is a protein, primary antibody is ligand, col. 13, lines 45-52), and the Raman-active probe construct comprising a secondary antibody as probe and a Raman tag (secondary antibody is antibody conjugated to Au, col. 13, lines 50-52). Natan et al. also teaches the Raman-active probe being a

composite organic-inorganic nanoparticle (organic portion is the secondary antibody conjugated to the inorganic portion of gold or silver particle; col. 15, lines 28-29).

With respect to claim 10, 14-17, Natan et al. teach a substrate coated with one or more organic or inorganic materials prior to immobilization of proteins (gold evaporated onto glass substrate, col. 24, lines 40-44). Natan et al. further teaches the substrate comprised of a plurality of discrete locations on a flat plate (wells, col. 24, line 66-col. 25, line 5), and detection automated to accomplish high throughput scanning at sequential discrete locations (col. 23, lines 63-66; col. 26, lines 39-48). Natan et al. also teaches the substrate comprising gold (gold evaporated on glass; col. 24, lines 41-44) and contacting the proteins at the discrete locations with silver nanoaparticles (col. 16, lines 45-53).

Regarding claims 21-26, Natan et al. teach the Raman spectra being a SERS spectra (col. 23, lines 58-61), and collecting the SERS spectra from the discrete locations to compile a protein profile of the sample (col. 25, lines 1-5). Natan et al. further teach collection being automated to accomplish high throughput SERS spectra screening of the discrete locations (SERS can be used as well as SPR using the PDMS microwell arrays for high throughput screening, col. 23, lines 58-61). Natan et al. also teach the spectrum containing information regarding a protein characteristic of identification of the protein (sensors are used to detect unique compounds, which can be proteins, col. 24, lines 1-5). The separated proteins are introduced into a flowing stream (col. 29, lines 29-52), therefore the proteins are maintained a separated state. A stream of metal colloids is further mixed under conditions suitable for formation of SERS-active nanoparticles with the stream (Au particles can alternatively be Ag, col. 16, lines 45-53; nanoparticles introduced into flow cell, col. 29, lines 4-52).

With respect to claims 29-33, Natan et al. teach a sample being a patent sample of blood (col. 15, lines 15-23). Natan et al. also teach creating a protein profile of the sample based on data obtained from the Raman spectra (col. 23, lines 58-61; col. 24, lines 1-6), and repeating the method using a variety of different patient samples to create a protein library containing a plurality of different protein profiles (sensor combine to form a library of ingredients, proteins, in the sample, col. 24, lines 4-6). Natan et al. further teach the comparing the protein profile of the sample with one or more protein profiles of the library to detect a difference indicative of a disease (asthma, col. 15, lines 23-31).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Grow (US 6,040,191).

Natan et al., as applied to claim 1, teach a method for analyzing protein content of a biological sample, but fails to teach denaturing proteins in the sample.

Grow teaches denaturing proteins in a sample (col. 11, lines 14-20 and 26-42), in order to determine different unique structures of biological conformation of a biological-analyte complex.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al., denaturing proteins before separation as taught by Grow, in order to prevent false responses due to proteins being denatured, inactivated, poisoned or leached.

Regarding claim 6, Grow teaches a biological-analyte, protein, solubilized in an aqueous solution (col. 20, lines 32-39).

With respect to claim 8, Grow teaches a denaturing agent being surfactants (col. 56, lines 28-31), and denatured proteins dried on a substrate prior to detection of signals (col. 25, line 56-col. 26, line 5).

7. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Avseenko et al. (Immobilization of Proteins in Immunochemical Microarrays Fabricated by Electrospray Deposition, Analytical Chemistry, 2001, 73, 6047-6052).

Natan et al., as applied to claim 1, teach a method for analyzing protein content of a biological sample without denaturing, but fail to teach separated proteins deposited using wet electrospray.

Avseenko et al. teach separated proteins deposited without denaturing using wet electrospray deposition (pg. 6048, right column, *Fabrication of Microarrays*, electrospray

deposition of protein) onto an aluminum substrate (pg. 6048, left column, *Materials*, aluminized mylar film), in order to fabricate protein microarrays for immunochemical analysis.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al., deposition of proteins without denaturing using wet electrospray deposition as taught by Avseenko et al., in order to reduce spot size, increase fabrication rate, and simultaneously manufacture thousands of identical microchips while retaining ability to specifically bind antibodies.

Avseenko et al. also teach less preferable alternatives to deposition of proteins including contact writing (microcontact printing, pg. 6047, last paragraph left column-first paragraph, right column).

8. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Storhoff et al. (US 2004/0053222).

Natan et al., as applied to claim 1, teach a method for analyzing protein content of a biological sample, but fail to teach contacting nanoparticles with at least one chemical enhancer salt.

Storhoff et al. teach gold nanoparticles contacted with at least one chemical enhancer salt of LiCl (paragraph 0049), in order to allow a sufficient number of additional polyanionic polymer conjugates, wherein the polymer conjugates are proteins (paragraph 0053), to bind to the nanoparticles.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al., nanoparticles contacted with a

solution containing at least one chemical enhancer salt as taught by Storhoff et al., in order to increase stability of nanoparticles while binding proteins.

9. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Nelson et al. (US 5,955,729).

Natan et al., as applied to claim 1, teach a method for analyzing protein content of a biological sample, but fails to teach analyzing separated proteins by mass spectroscopy.

Nelson et al. teach performing surface plasmon resonance-mass spectroscopy by detecting particles using SPR to detect the changes in the refractive index of the solution close to the surface of the sensor chip, and analyzing separated proteins by mass spectroscopy, to identify the presence of nontargeted ligands and to correct them for quantitative techniques.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al., analyzing separated proteins by mass spectroscopy as taught by Nelson et al., in order to quantify the amount of analyte in the sample and to provide real-time information regarding molecular interactions.

Nelson et al. teach compiling data from the mass spectroscopy with data from SPR (Fig. 4, relative intensity and resonance signals are compared, col. 4, lines 58-64), and according to Natan et al. an SERS measurement can be used instead of an SPR measurement in order to accommodate other surface-sensitive analytical techniques (col. 23, lines 54-61).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Yu whose telephone number is (571) 272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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03/04/05